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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/642,660	08/22/2000	Jonathan Schneck	01107.00042	9271

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EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 08/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/642,660	SCHNECK ET AL.	
	Examiner	Art Unit	
	Christopher H. Yaen	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-32 and 51-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-32 and 51-58* is/are rejected.

7)☒ Claim(s) *59 and 60* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Re: Schneck *et al*

1. Upon further review and reconsideration, the finality of the last office action is withdrawn in view of the newly applied rejections set forth herein.

2. The amendment filed 3/8/2005 is acknowledged and entered into the record. Accordingly, claims 1-27 and 33-50 are canceled without prejudice or disclaimer.

3. Claims 28-32 and 51-60 are pending and examined on the merits.

Claim Rejections Maintained - 35 USC § 112, 1st paragraph

4. The rejection of claims 32, and 52-58 under 35 USC § 112, 1st paragraph as lacking adequate written description is maintained for the reasons of record. Applicant argues that the written description in this case for the antigenic peptides has been adequately described. Specifically, applicant argues that what is well known or taught in the art need not be described in the instant specification. To support his assertion applicant indicates that the antigenic peptides are well known to the skilled artisan as those peptides that are generated by endosomal/lysosomal digestion and further cites Abbas *et al*, who teaches that general functional characteristics of antigenic peptides. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record.

The written description guidelines indicate that for adequate written description of a claimed invention, the specification must disclose structural and functional

characteristics coupled with a known or disclosed correlation between function and structure. Moreover, to provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus, by describing a representative number of species that is representative of the claimed genus. In the instant case, applicant has not described any correlation between structure and function, nor has the applicant disclosed a common characteristics linking the claimed genus of "antigenic peptide" so that the skilled artisan could identify members of the genus. Applicance reliance on general teachings is not sufficient, because what is needed is specific disclosure. The skilled artisan thus cannot envision the detailed chemical structure of the encompassed genus of polypeptides, regardless of the complexity or simplicity of the method of isolation. The claims do not require any particular function, other than the generic function of eliciting an antigenic response, that would serve to identify the molecules encompassed by the genus so that one of skill would recognize that Applicant was in possession of them. Applicant has also not identified any specific core region that is responsible of the antigenic peptide so as to rely on the general disclosures to encapsulate the genus.

Therefore, the rejection of the claims under 35 USC §112, 1st paragraph, written description is maintained for the reasons of record.

New Rejections

Claim Rejections - 35 USC § 103

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 28-31 and 51-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsui et al (Proc. Natl. Acad. Sci., USA, 91(26)12862-12866, 20 December 1994) in view of Dal Porto et al (Proc. Natl. Acad. Sci., USA, 90(14):6671-6675, 15 July 1993, previously cited) and Chang et al (Proc. Natl. Acad. Sci., USA, 91(24):11408-11412, 22 November 1994previously cited) and Harris et al (WO 94/09131, 4/28/1994).

Claims are drawn to a cellular composition comprising a molecular complex bound to the surface of the cell, wherein the molecular complex comprises a first and a second fusion protein, wherein said first fusion protein comprises an immunoglobulin heavy chain variable region (IgG1) and the extracellular domain of an MHC class IIβ chain or TCRα chain (extracellular domain of a first transmembrane polypeptide), wherein said heavy chain variable region and said MHC class IIβ chain or TCRα chain are connected by a first peptide linker, and said second fusion protein comprising an immunoglobulin light chain (Igk) and the extracellular domain of an MHC class IIα chain or TCRβ chain (extracellular domain of a second transmembrane polypeptide), wherein said immunoglobulin light chain (Igk) and said MHC class IIα chain or TCRβ chain are connected by a second peptide linker, whereby two first and two second fusion proteins associate to form a first molecular complex comprising at least four fusion proteins,

comprising two ligand binding sites (i.e., divalent), each ligand binding site formed by the extracellular domain of the first and second transmembrane polypeptides (i.e., MHCIIα-MHCIIβ and TCRα-TCRβ), wherein the first molecular complex (divalent) has increased affinity for its ligand relative to a second molecular complex consisting of the extracellular domain of a first transmembrane polypeptide and the extracellular domain of the second transmembrane polypeptide (i.e., monovalent).

a. Matsui *et al* teach that despite the availability of monovalent forms of TCRs and MHC heterodimers, the interaction between these two molecules has been difficult to study directly due to the very low affinity (see abstract). Matsui *et al* teach that the interaction between monovalent TCR and MHC (class II MHC molecule I-E^k) heterodimers is a low affinity interaction, characterized by a slow association rate and a fast dissociation rate (see page12862, right column and Table 1 and Figure 2). Matsui *et al* do not specifically teach a method of making divalent TCR/IgG and class II MHC/IgG molecules, wherein both immunoglobulin heavy and light chains are linked at their N-termini to the extracellular binding domains of the TCR or class II MHC molecule. This deficiency is made up for in the teachings of Dal Porto *et al* and Chang *et al* and Harris *et al*.

b. Dal Porto *et al* teach a method for producing divalent high-affinity class I MHC/IgG molecules for studying cell-cell interactions and Dal Porto *et al* suggests that divalent MHC/IgG molecules are good candidates for high-affinity MHC-like molecules that could be used to selectively suppress specific T cell responses (see pages 6672 and 6675 and Figure 1B). Dal Porto *et al* teach

divalent class I MHC/IgG molecules (H-2K^b/IgG) that demonstrate nanomolar affinities for T cell receptors and nanomolar concentrations of the divalent H-2K^b/IgG molecule specifically inhibited lysis of target cells by alloreactive H-2K^b-specific T cells, whereas monovalent H-2K^b never inhibited the response of alloreactive H-2K^b-specific T cells to cells expressing native H-2K^b molecules and previous indirect measurements of the interaction between monovalent MHC class I and T cells suggests affinities in the micromolar range (see abstract and pages 6674-6675).

c. Chang *et al* teach that the generation of TCR molecules is hampered by inefficient pairing of α and β subunits in the absence of their respective transmembrane regions and Chang teaches that fusion of peptide sequences known to form unique heterodimeric coiled-coils to the C-termini of the TCR α and β extracellular segments promotes heterodimer formation over homodimer formation (see entire document, particularly abstract, pages 11408, 11410-11411 and Figs. 2A and 3A).

d. Harris *et al* teaches methods for producing bivalent (i.e., divalent) binding proteins comprising fusing binding domains via a linker to the N-terminus of the variable regions of the heavy chain and the light chain and the fusion proteins retain binding activity and the binding domains can include cell surface receptors (see entire document, particularly pages 6-8, page 12, lines 15-19 and page 13, lines 7-16 and Figures 2, 6, 8 and 9). Harris *et al* teach that the genes encoding

the fusion proteins can be expressed from one vector or from two different vectors (see page 29, lines 7-13).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a high affinity divalent TCR/IgG and class II MHC/IgG molecules for selectively suppressing specific T cell responses and for studying cell-cell interactions in view of Matsui *et al* and Dal Porto *et al* and Chang *et al* and Harris *et al*.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a high affinity divalent TCR/IgG and class II MHC/IgG molecules for selectively suppressing specific T cell responses and for studying cell-cell interactions in view of Matsui *et al* and Dal Porto *et al* and Chang *et al* and Harris *et al* because Matsui *et al* teach that the interaction between monovalent forms of TCRs and MHC heterodimers has been difficult to study directly, due to the very low affinity between these molecules and Dal Porto *et al* teach a divalent class I MHC/IgG molecule (H-$2K^b$/IgG) having nanomolar affinity for T cell receptors and nanomolar concentrations of the divalent H-$2K^b$/IgG molecule specifically inhibited lysis of target cells by alloreactive H-$2K^b$-specific T cells, whereas monovalent H-$2K^b$ never inhibited the response of alloreactive H-$2K^b$-specific T cells to cells expressing native H-$2K^b$ molecules and the interaction between monovalent MHC class I and T cells suggests affinities in the micromolar range. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was

made to have produced a method for making high affinity divalent TCR/IgG and class II MHC/IgG molecules for selectively suppressing specific T cell responses and for studying cell-cell interactions in view of Matsui *et al* and Dal Porto *et al* and Chang *et al* and Harris *et al* because Chang *et al* teach the generation of TCR molecules is hampered by inefficient pairing of α and β subunits in the absence their respective transmembrane regions and Chang teaches that fusion of peptide sequences known to form unique heterodimeric coiled-coils to the C-termini of the TCR α and β extracellular segments promotes heterodimer formation over homodimer formation and according to Chang this approach makes it possible facilitate the association of any type of naturally occurring heterodimeric structure including MHC class II α and β subunits (see page 11412, right column) and Harris *et al* teach that binding domains can be fused via a linker to the N-terminus of the variable regions of immunoglobulin heavy and light chains without altering the binding function of the fusion proteins. Therefore, the ordinary skilled artisan would have been motivated at the time the invention was made to express one TCR/MHC class II extracellular binding domain as a fusion protein with the immunoglobulin heavy chain and express the other TCR/MHC class II extracellular binding domain as a fusion protein with the immunoglobulin light chain in order to facilitate pairing and proper folding of the α and β polypeptides of the TCR and MHC class II molecules and one of ordinary skill in the art would have had a reasonable expectation of success because Harris demonstrates that binding domains can be fused via a linker to the N-terminus of the variable regions of immunoglobulin heavy and light chains without altering the binding function of the fusion proteins. Further, one of

ordinary skill in the art at the time the invention was made would have been motivated to have produced high affinity divalent TCR/IgG and class II MHC/IgG molecules to overcome the intrinsic low affinity of TCR and MHC heterodimers (monovalent), which has limited their use. Thus, it would have been obvious to one skilled in the art at the time the invention was made to have produced a high affinity divalent TCR/IgG and class II MHC/IgG molecules for selectively suppressing specific T cell responses and for studying cell-cell interactions in view of Matsui *et al* and Dal Porto *et al* and Chang *et al* and Harris *et al*.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

No claim is allowed. Claims 59-60 are objected to as being dependent upon a rejected base claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H. Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1643
July 26, 2005

SHEELA HUFF
PRIMARY EXAMINER